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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,696	02/03/2006	Giorgio Bertolini	2003IT303	3884

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PROPAT, L.L.C.
425-C SOUTH SHARON AMITY ROAD
CHARLOTTE, NC 28211-2841

EXAMINER	
BLAND, LAYLA D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,696	BERTOLINI ET AL.	
	Examiner	Art Unit	
	Layla Bland	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/22/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/3/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a national stage entry of International Application No. PCT/IB04/02520, filed July 29, 2004, and claims priority to Italian Application No. MI2003A01610, filed August 5, 2003. Claims 1-16 are pending in this application and are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "natural or modified...purine or pyrimidine base." Neither the claim nor the specification define how the purine or pyrimidine base may be modified, which renders the claim indefinite. One of ordinary skill in the art would not be apprised of which modifications are encompassed by the claim.

Claims 2, 9 and 16 are drawn to the process of claim 1 wherein P' can be a group $R_1COOC(R_2R_3)$- in which R_1, R_2 and R_3 represent a C_1-C_6 alkyl. The specification, page 8, lines 9 and 10, gives a preferred example as 5'-(2-acetoxybutyryl)-2',3'-didehydro-2',3'-dideoxyinosine (formula I wherein $P=CH_3COOC(CH_3)_2CO$-). It is assumed that the above mentioned limitation in claims 2,

9, and 16 refer to this embodiment; however, the two formulae do not match and neither corresponds to a 2-acetoxybutyryl group. Clarification is requested.

Claims 1, 2, 10, and 11 (and all dependent claims) recite the limitation "optionally substituted." "Optionally substituted" is not defined by the claim or the specification and renders the claim indefinite because it can include substituents which are not actually disclosed and one of ordinary skill in the art would not know what the substituents are.

Claim 12 is drawn to the process of claim 1, wherein the 2',3'-didehydro-2',3'-dideoxynucleoside can be dideoxyadenosine. Dideoxyadenosine is not a 2',3'-didehydro-2',3'-dideoxynucleoside; there is insufficient antecedent basis for this limitation in the claim.

Claim 13 is drawn to the process of claim 1, wherein B can be inosine. Claim 1 defines B as a purine or pyrimidine base or heterocyclic system comprising a nitrogen atom. Inosine is a nucleoside that is formed from hypoxanthine and is a likely starting material for formula (II). It is unclear whether inosine was actually intended in the claim. Clarification is requested.

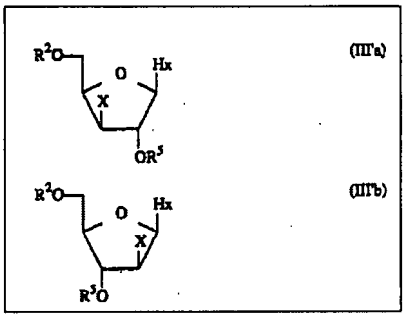
Claim Rejections - 35 USC § 103

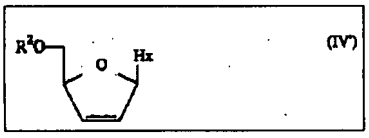
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

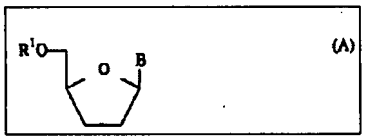
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honda et al. (US 5,466,793, November 14, 1995, PTO-1449 submitted February 3, 2006) in view of Hrishikesan (US 3,445,186, May 20, 1969).

Honda et al. teach a process for preparing 2',3'-dideoxyinosines [abstract]. The nucleoside can be unprotected (P=H) or protected with a C_{1-12} acyl group, a C_{1-12} alkyl group, a C_{7-8} aryl group, or a silyl group [column 4, lines 40-44]. An inosine derivative III'a or III'b, shown below [column 5, lines 45-55], is allowed to react with zinc powder in the presence of acetic acid in an organic solvent. [column 8, line 65 – column 9, line 15] The zinc complex formed in the reaction must be removed because it can interfere with subsequent reactions and forms zinc hydroxide gel when treated with water, which is difficult to remove [column 10, lines 28-38]. The zinc powder is removed by ion-exchange resin, porous nonpolar resin, or chelating agent to give the corresponding 2',3'-didehydro-2',3'-dideoxy-5'-O-acylinosine. The organic solvent used in the reaction can be methanol, ethanol, acetonitrile, THF, DMF, or a mixture thereof. [column 8, line 65 – column 9, line 15] The 2',3'-didehydro-2',3'-dideoxynucleoside inosine derivative IV', shown below [column 5, lines 35-40], obtained by the zinc reaction, is then subjected to reduction with hydrogen over palladium catalyst, followed by hydrolysis or ester exchange reaction to give 2',3'-dideoxyinosine derivative A', shown below [column 5, lines 15-20]. [column 9, lines 16-21]







In one example, 9-(2',5'-O-diacetyl-3'-bromo-3-deoxy-β-D-xylofuranosyl)hypoxanthine and 9-(3',5'-O-diacetyl-2'-bromo-2'-deoxy-β-D-cylofuranosyl)hypoxanthine was suspended in a mixture of 25 ml acetonitrile and 25 ml methanol, zinc powder, and acetic acid, and stirred for one hour. After workup, 5'-O-acetyl-2',3'-didehydro-2',3'-dideoxyinsoine was obtained. This product was suspended in ethanol, Pd-$BaCO_3$ was added, and the mixture was stirred for two hours under a hydrogen gas stream to give 5'-O-acetyl-2',3'-dideoxyinosine. [Column 19 and 20, Examples 3 and 4]. In another example, sodium hydroxide was used to deprotect the product after hydrogenation to give 2',3'-dideoxyinosine [column 20, Example 5]. In another example, the product of the zinc reduction is partially deprotected during the workup, before the hydrogenation reaction [column 20, Example 6].

Honda et al. do not teach removal of zinc using an alkali metal sulfide or an alkaline-earth metal sulfide.

Hrishikesan teach the removal of dissolved zinc from alumina hydrate by adding at least a stoichiometric amount of alkali metal sulfide to cause precipitation of the zinc as zinc sulfide [see abstract]. Sodium sulfide effects the precipitation of zinc as zinc sulfide, which is filtered off [column 2, lines 7-25]. An excess of alkali metal sulfide, such as sodium or potassium sulfide, is preferred [column 2, lines 46-54]. Aqueous solution of sodium sulfide was used [column 4, Example 2].

It would have been obvious to one of ordinary skill in the art at the time the invention was made employ sodium sulfide for the removal of zinc in the method taught by Honda et al. Honda et al. teach that excess zinc must be removed from the reaction, and Hrishikesan teaches a method of precipitating zinc as zinc sulfide, which can then be filtered off. The skilled artisan would understand that the zinc removal steps used in the method of Honda et al. and the sodium sulfide zinc removal taught by Hrishikesan could be used interchangeably to arrive at the same result (removal of zinc from the reaction mixture). One of ordinary skill in the art would also understand that removal of the 5' protecting group could be carried out either before or after the hydrogenation reaction and would not be expected to impact the reaction.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Honda et al. (US 5,466,793, November 14, 1995, PTO-1449 submitted February 3, 2006) in view of Hrishikesan (US 3,445,186, May 20, 1969) as applied to claims 1-13, 15 and 16 above, and further in view of Bertolini et al. (WO 01/77103 A1, October 18, 2001).

Honda et al. and Hrishikesan teach as set forth above.

Honda et al. do not teach the use of ammonium salt or phosphonium salt as activating agents in the zinc reaction.

Bertolini et al. teach a process wherein 2'-deoxy-2'-bromo-3',5'-diacetyl-5-methyluridine is converted into 5'-acetylstavudine by reductive elimination in the presence of zinc as reducing agent combined with an ammonium salt or phosphonium salt as the activating agent [page 2, lines 5-11].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use ammonium salt or phosphonium salt as the activating agent, instead of acetic acid, in the method of Honda et al. Both Honda et al. and Bertolini et al. teach reductive elimination using zinc in the presence of an activating agent, but each of the references teaches a different activating agent. The skilled artisan would understand that the reactions taught by Honda et al. and Bertolini et al. are analogous reactions and that the activating agents could be used interchangeably and successfully in the zinc reaction.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the

claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Bland whose telephone number is (571) 272-9572. The examiner can normally be reached on M-R 8:00AM-5:00PM UST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Layla Bland
Patent Examiner
Art Unit 1623
October 15, 2007

Shaojia Anna Jiang

10/18/07

Supervisory Patent Examiner
Art Unit 1623
October 15, 2007